#15
6-20-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: BRONK, ET AL. :

APPLICATION NO.: 09/424,104 : Examiner: PESELEV, E.

FILING DATE: NOVEMBER 18, 1999 : Group Art Unit: 1623

TITLE: 4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES :

Assistant Commisioner for Patents
Washington, D.C. 20231

Sir:

Declaration Pursuant to 37 CFR §1.132

I, Brian S. Bronk, am a citizen of the United States, residing at 66 Partridge Hollow Road, Gales Ferry, Connecticut, U.S.A., and I declare as follows:

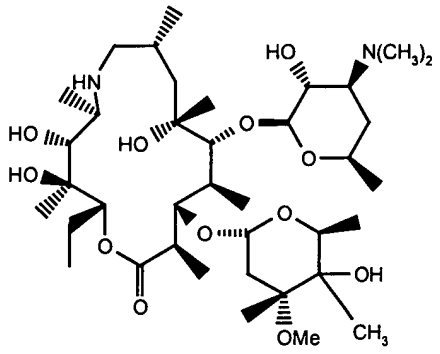
1. I am one of the above-identified co-inventors named in the subject application.

2. I obtained a Ph.D. degree in Chemistry from Massachusetts Institute of Technology, Massachusetts, U.S.A. I have been employed by Pfizer Inc. since October 1994.

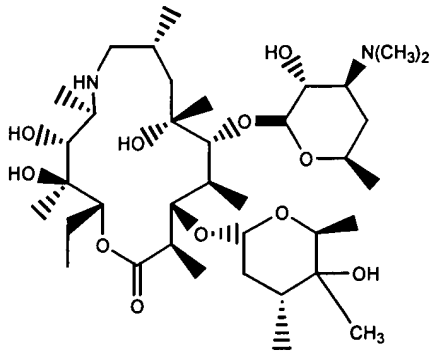
3. I have read the Office Action dated January 8, 2001 concerning the subject application.

4. I understand that this is being submitted to show the surprising antibacterial activity as illustrated by *in vivo* mouse PD50 data of the compounds of the present application.

5. Based on *in vivo* mouse PD50 data that was generated using the experimental protocol described in attached exhibit 1, a representative compound of the present invention, referred to herein as compound 1, showed surprisingly better antibacterial activity when compared to a compound containing the ring structure of Hauske that was modified with a 4" substituent described by Yang et al. These compounds and their PD50 values are shown below.



Representative compound 1 of the present invention
Mouse PD50 = 28 mg/kg



Compound 2 (Hauske modifed with Yang 4" substituent)
Mouse PD50 > 80 mg/kg

6. The above data show that substituting at least one of the 4" substituents described by Yang et al into the ring structure of Hauske does not result in a compound (compound 2) exhibiting commercially acceptable antibacterial activity.

7. Since at least one of the 4" substituents described by Yang et al. does not, when substituted into the ring structure described by Hauske, provide adequate antibacterial activity (as illustrated by *in vivo* mouse PD50 data), it would not be reasonable to expect, based on the descriptions of Yang et al and Hauske, that all or

any of the Yang et al substituents would, if substituted into the ring structure described by Hauske be expected to show antibacterial activity.

8. Further, it was therefore unpredictable at the time of the present invention as to which, if any, of the 4" substituents described by Yang et al, i.e., alkyl, alkenyl or phenyl groups, or a hydrogen and a specified amino derivative (column 2 lines 40 to 65 of Yang et al) would, if substituted into the ring structure described by Hauske, provide for compounds exhibiting antibacterial activity (as illustrated by *in vivo* mouse PD50 data).

9. The undersigned inventor declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Signed: 

Brian S. Bronk

Date: 6/12/2001

Exhibit 1

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3 x 10^3 CFU/ml bacterial suspension (*P. multocida*) strain 59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1X challenge dose and two infected with 1X challenge dose; a 10X challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral doses. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge. The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.